On page 65, line 10, please insert (SEQ ID No. 5) after the word "(405-425)".

On page 65, line 11, please insert (SEQ ID No. 6) after the word "(687-663)".

REMARKS

The following comments are directed toward the Final Office Action of July 16, 1998. Claims 1-20 are pending currently. No new matter has been added. Reconsideration of this application in view of the remarks and the amendments *supra* is respectfully requested.

The 35 U.S.C. §102(b) Rejection:

Claims 1-4, 6-11 and 13-20 stand rejected under 35 U.S.C. §102(b) as being anticipated by **Cummins, Jr.** (U.S. Patent 5,019,382). This rejection is respectfully traversed.

The Examiner directs cites the following portions of the **Cummins** patent to support this rejection: column 4, lines 19-36, col. 5, lines 50-55, col. 6, lines 12-26, col. 13 and the claims. Column 4, lines 19-36 discuss the types of disease conditions in which the **Cummins** patent might be employed, namely: "...apparent autoimmune disorders characterized by a chronic tissue degenerative

inflammatory condition. Diseases so characterized include multiple sclerosis, rheumatoid arthritis, stomatitis, and lupus erythematosus." Conditions supported by actual clinical data in the prior art are predominantly veterinary diseases, such as two cases of purported "canine lupus erythematosus".

Of the human cases pertaining to autoimmune conditions, there is only one anecdotal report of a multiple sclerosis patient that had been treated. The remainder are cases that are either clearly not autoimmune conditions (cancers, acne, viral warts) or maladies for which an autoimmune etiology remains controversial (rheumatoid arthritis, stomatitis).

Applicant argues this limited clinical data is far from enabling and hence cannot be considered anticipatory. **Cummins** describes in column 12 that a female with multiple sclerosis "received treatment in accordance with the present invention" and "had no recurrence...for the past nine months". Apart from the consideration that such a disorder is characterized by remission and relapse, as is known in the art, **Cummins** provides absolutely no credible evidence that such an invention could be made or was in fact made. Similarly, the **Cummins** descriptions of treating malignant lymphoma, mesothelioma and apthous stomatitis are also anecdotal. A person

having ordinary skill in this art would consider these anecdotal descriptions as literally incredible and therefore non-enabling.

As the Supreme Court held in *Seymour v. Osbourne*, 78 U.S. (11 Wall.) 516 (1870) a non-enabling reference is not anticipatory prior art under 35 USC § 102. See, also, *Akzo N.V. v. U.S. Int'l Trade Comm'n*, 1 USPQ2d 1241 (Fed. Cir. 1986); *In re Wiggins*, 179 USPQ 421 (CCPA 1973); *In re Brown* 141 USPQ 245 (CCPA 1964). That is, to be an anticipatory reference under 35 USC §102, the prior art must be enabling to the same degree as an invention seeking patent protection under 35 U.S.C §112, first paragraph.

The instant invention targets a much broader spectrum of autoimmune conditions than **Cummins**, and, more importantly, presents substantive clinical data in support. In marked contrast to the one multiple sclerosis patient presented in **Cummins**, the instant specification contains data from 27 multiple sclerosis patients and 18 control patients. Animal data presented is that of a very well established model of human autoimmune disease, experimental allergic encephalitis/neuritis.

Further, the **Cummins** claims are limited to treating viral diseases. Applicant respectfully submits that the claimed invention falls outside the scope of the **Cummins** disclosure. **Cummins** repeatedly emphasizes the criticality of maintaining the interferon in

contact with the oral and pharyngeal mucosa for the purposes of treating viral diseases. The claims under examination specifically point out that Applicant's method requires ingestion of the interferon. Indeed, Applicant's specification shows the necessity of the interferon interacting with intestinal sites and Peyer's patches.

The section of **Cummins** cited by the Examiner (col. 4, lines 19-36) in support of the under 35 U.S.C. §102(b) also presents the suggested dosage for the therapeutic agent. This is much different than the one presented in the instant invention—"...more preferably 0.5 to about 1.5 IU/lb of body weight per day" as compared to 50 –25,000 IU/kg every other day.

With respect to the route of administration presented in col. 4, lines 19-36, Claim 1 of the instant invention states: "A method of treating an auto-immune disease in an animal comprising the step of orally administering a type one interferon to said animal **such that the type one interferon is ingested after oral administration.**" (emphasis added). This is clearly distinct from **Cummins** which emphasizes a different mode of absorption:

> ...in a dosage form adapted to promote contact of said dosage of interferon with the oral and pharyngeal mucosa of said animal. (emphasis added).

As one of the accompanying 37 CFR Rule 1.132 Declarations points out, **Cummins** "stresses that administration of interferon should be directed at absorption through the oral mucosa, and not the gastric mucosa. Maximal contact with the oral or pharyngeal mucosa is emphasized, contact with the gastric or intestinal mucosa is considered therapeutically nugatory." This is contrasted with Applicants' invention, in the other accompanying 37 CFR Rule 1.132 Declaration: "In Applicant's animal experiments, **the interferon was fed through a needle inserted directly into the stomach or duodenum of the animal, i.e., there was no contact with the oral or pharyngeal mucosa.** In Applicant's clinical studies with human subjects, the interferon was "ingested", which briefly exposed the oral mucosa to the interferon, but **no attempts at maximizing contact with the oral mucosa were made nor would there have been any significant absorption of the alpha-interferon through the oral or pharyngeal mucosa**." (emphasis added).

Examiner cites col. 5, lines 50-55 of **Cummins** supporting the rejection of claims 1-5 and 6-7 under 35 U.S.C. §102(b). This section teaches the dosage of the therapeutic agent, viz.:

"Daily dosage of interferon can be administered as a single dosage, or, preferably, it is divided and administered in a multiple-dose daily regimen. A staggered regimen, for example one to three days treatment per week or month, can be used as an alternative to continuous daily treatment." (emphasis added).

Applicant contends that this does not anticipate the instant invention, as it teaches a multiple-dose daily regimen. Additionally, the descriptive clinical lore of the **Cummins** patent can does not anticipate Applicant's substantive data.

Examiner further cites col. 6, lines 12-26 of **Cummins** to support the rejection of Claims 1-5 and 6-7 under 35 U.S.C. §102(b). Applicant argues that this is an explicit teaching away from the present invention. Lines 12-16 of col. 6 make this point clearly:

"It is also contemplated by the present invention to provide interferon in a solid dosage form such as a lozenges (sic) adapted to be dissolved upon contact with saliva in the mouth with or without the assistance of chewing."

As stated in the Specification, the interferon dosage of the instant invention can be said to by-pass the mouth, see, e.g. Example 11. As stated *supra*, in the method of the instant invention,

interferon is orally administered by placing a 2.5 cm syringe fitted with a 20 gauge ball point needle in the posterior oropharyngeal region of the oral cavity and delivering the type one interferon dose directly to the distal esophagus, stomach, and proximal small intestine (as verified experimentally by injecting Evans blue during routine feeding and subsequent sacrifice).

Column 13 of the **Cummins** patent is also cited in support of the §102(b) rejection. Column 13 lists the various ways in which the interferon dosages can be formulated, e.g. lozenges, chewable vitamins etc. Again, this can be read as teaching away from the instant invention as all formulations are so constructed as to maximize the contact of the interferon with the oropharyngeal mucosa, in contrast with Applicant's invention.

Thus, Applicant maintains that there are such substantive differences between the method of **Cummins** and the claims presented in the instant invention that the **Cummins** patent in no way anticipates the current claims. Declarations under 37 CFR 1.132 are provided herewith, which support and extend Applicant's arguments. Accordingly, Applicant respectfully requests that the rejection of Claims 1-4, 6-11 and 13-20 under 35 U.S.C. §102 as being anticipated by **Cummins** be withdrawn.

The 35 U.S.C. §103 Rejections:

Claims 5 and 12 stand rejected under 35 U.S.C. §103 as being unpatentable over **Cummins, Jr.** (US Patent 5,019,382). This rejection is vigorously traversed. As stated above, **Cummins** teaches the dosage of the therapeutic agent:

> "Daily dosage of interferon can be administered as a single dosage, or, preferably, it is divided and administered in a multiple-dose daily regimen. A staggered regimen, for example one to three days treatment per week or month, can be used as an alternative to continuous daily treatment." (emphasis added).

Applicant contends that the dosage regimens of Claims 5 and 12 are not rendered obvious by **Cummins**. The instant invention teaches an every other day dosing. This is alluded to as a less preferred method of administering interferon by **Cummins,** which teaches a multiple-dose daily regimen.

Examiner further states that claims 1-20 stand rejected under 35 U.S.C. §103 as being unpatentable over **Cummins** in view of **Shibutani et al**. This rejection is respectfully traversed.

Applicant respectfully asserts that the cited references do not render the present invention obvious under 35 U.S.C. Section §103

for the reasons cited above in response to the 35 U.S.C. Section §102 rejection. The **Shibutani** abstract is simply a description of a lack of toxicity of human beta interferon in mice and rats. It does not disclose, teach or suggest in any form a method of treating auto-immune disease in an animal comprising the step of orally administering a type one interferon to said animal such that the type one interferon is ingested after oral administration as disclosed in the instant application.

This issue of dosage is addressed in some detail in both Rule 1.132 Declarations, the most salient aspects of the arguments are recapitulated here. First, it is emphasized that one very valuable feature of the instant invention is its precise and meticulous delineation of a dose-response relationship for the oral administration of type I interferons to treat autoimmune diseases. This relationship is somewhat exceptional. Secondly, there is absolutely no overlap between the doses suggested by **Cummins** and doses found to be effective in the present invention. The latter are significantly higher (by about two orders of magnitude) than the maximum dose of **Cummins**.

As both Rule 1.132 Declarations point out, **Cummins** describes unsubstantiated anecdotal stories which essentially do not enable Applicant's invention and place Applicant's invention in the

hands of a person having ordinary skill in this art. A person with ordinary skill in the art would not likely believe **Cummins'** rhetoric regarding the importance of contact with the oropharyngeal mucosa and nor would a person having ordinary skill in this art be motivated to make the instant invention. Hence, no such teaching, suggestion or incentive may be gleaned from the references relied upon by the Examiner. Thus, Applicant respectfully submits that the cited references do not render the claimed invention obvious. Accordingly, Applicant respectfully requests that the rejection of Claims 1-20 under 35 U.S.C. §103 be withdrawn.

The 35 U.S.C. §112 Rejections:

Claims 1-12 and 19-20 stand rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey that the inventors were in possession of the invention at the time the application was filed.

With respect to the §112 rejection, Examiner writes: "Although there may be a patentable difference between Cummins and the instant invention, applicant has failed to establish clear and convincing evidence that there is a patentable difference." Applicants contend that the arguments supra for the §102 and §103

rejections, buttressed by the 37 CFR Rule 1.132 Declarations, clearly suffice to establish a patentable difference between the two. Accordingly, in view of Applicant's remarks, Applicant respectfully requests that the rejection of Claims 1-12 and 19-20 under 35 U.S.C. §112, first paragraph, be withdrawn.

This is intended to be a complete response to the Final Office Action mailed July 16, 1998. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

Date: Nov 17, 1998

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